Allergy Abstracts

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Asthma and Hay Fever

Treatment of Hay-Fever With Hydrocortisone Snuff. Herxheimer, H., and McAllen, M.: Lancet **1**: 537, 1956.

The authors treated 24 severe cases of grass pollen sensitivity intranasally with hydrocortisone powder. The patients (14 males and 10 females) ranged in age from 14 to 35 years and had responded poorly to antihistamine therapy. None of the patients had received desensitization therapy during the previous 12 months. The hydrocortisone was ground very finely and placed in a capsule. Each capsule contained 15 mg. of hydrocortisone and 85 Gm. of lactose. The capsule was pierced and then placed into an insufflator which produced a fine spray. Patients were instructed to take the full contents of one capsule each day in 3 divided doses. When the tissues were so congested that the powder could not reach the inner portions of the nasal mucous membrane, Privine was used to shrink the tissues prior to inhalation of the powder. The inhalations were carried out for 5 days and then discontinued in order to determine whether or not symptoms would recur. Patients who had previously

obtained partial control of symptoms from antihistamines were permitted to continue taking them. Patients tolerated the spray very well and no side effects were noted.

All but one of the patients obtained excellent relief with hydrocortisone snuff within 10 days and most were markedly relieved within 48 hours. The slower responses occurred in the patients with rhinorrhea so profuse that they had difficulty in absorbing the powder. Only 2 of 19 patients who continued on the medication for the entire season had relapses. After 5 days of treatment many patients remained asymptomatic for another 9 to 10 days. Some were able to discontinue the medication permanently after 2 to 3 weeks of continuous therapy. Most of the patients with allergic conjunctivitis were remarkably relieved. Out of 10 patients who gave a history of pollen asthma, 4 were asymptomatic while on the hormone. No placebo powders were employed in these studies. The intranasal use of hydrocortisone is recommended as a safe and effective method of treatment of seasonal allergic rhinitis.

R. W.

Chronic Asthma Treated With Aerosol Hydrocortisone. Brockbank, W., Brebner, H., and Pengelly, C. D. R.: Lancet **2**: 807, 1956.

The authors used the "double blind" approach in treating 9 chronic nonseasonal asthma patients with inhalations of aerosol hydrocortisone. Neither the patient nor the doctor knew the contents of the aerosol until the study was completed. A 2 ml. solution containing sterile water, chlorbutanol, and 0.1 per cent Triton (a nontoxic surfactant) was used as a diluent for 100 mg. of hydrocortisone. A similar solution containing lactose was employed as a placebo. The patients were instructed to use the inhaler three times daily and to adjust the amount of spray so that the 2 ml. quantity would last one week. They were given a fresh supply of 2 ml. allotments each week for 10 weeks and were then kept under observation for another month. Patients who had been taking antispasmodic medication before starting the study were allowed to continue on it but were asked to keep a record of how much they took. They were also instructed to keep a careful check on the frequency and duration of their attacks. The hydrocortisone aerosol appeared to be less effective than the placebo and the authors concluded that this type of therapy was useless in the treatment of chronic asthma. R. W.

Reproducible Psychogenic Attacks of Asthma: A Laboratory Study. Dekker, E., and Groen, J.: J. Psychosomat. Res. **1**: 58, 1956.

The capacity of psychogenic stimuli to induce attacks of bronchial asthma was studied experimentally in 12 patients. The vital capacity of each patient as measured at 4-minute intervals and a base-line value was obtained. An emotional stimulus which was suggested by the patient's history was then administered. The test was considered positive if it was followed by a regular reduction in vital capacity of more than 10 per cent of the base-line value. The histories revealed that one woman got a sense of constriction merely by looking at dust, but only during the hay fever season. One asthmatic boy became dyspneic when he saw dust particles floating in the sunlight; when there was no sunshine, he had no symptoms. A jewelry salesman frequently became dyspneic when lifting his sample bag. A woman suffered an attack of asthma whenever she used an elevator. A young woman felt suffocated when she visited her father's grave, but only when her mother was present. Another

patient was so hypersensitive to aspirin that watching someone else swallowing an aspirin tablet gave her a feeling of suffocation. Looking at goldfish in a bowl caused an asthmatic attack in two patients.

After exposure to such stimuli, three patients developed definite asthmatic attacks accompanied by a pronounced decrease in vital capacity. Three patients showed a transient decrease in vital capacity accompanied by minor symptoms and signs. Six patients failed to react. These psychogenic attacks were distinguishable from "spontaneous" attacks of asthma or from attacks provoked by the inhalation of allergens. The attacks could be aborted by the administration of isoprenaline or thiacinamine. Since the knowledge of the artificiality of the experimental situations did not prevent the onset of asthmatic attacks, the authors suggest that these phenomena involve a process of acquired conditioning. M. C.

Dermatology

Physical and Physiological Clues for Diagnosing Eczema. Lobitz, W. C., Jr., and Dobson, R. L.: J. A. M. A. **161**: 1226, 1956.

Certain physical findings are found to be rather characteristic of patients who have or are prone to develop atopic dermatitis. Pallor is present, especially over the long prominences of the face. A tired expression about the eyes, probably caused by a hyperpigmented fold of skin of the lower eyelid, is present. Excessive dryness of the skin occasionally leads to ichthyosis, follicular hyperkeratosis, and chapping. An increased number of fine lines and markings are present in the palms. Exposure to emotional heat stimuli is frequently followed by cholinogenic urticaria.

The skin of these individuals demonstrates many abnormal physiological reactions. The cutaneous vascular reaction is extremely labile. There is often marked vasospasm, which accounts for the pale appearance of the skin. Intracutaneous injections of histamine often fail to produce the flare of the axon reflex. This can be attributed to vasoconstriction. The normal triple response fails to occur when severely involved skin is stroked, and only the white line of vasospasm occurs. This finding is considered to be an excellent diagnostic and prognostic sign, since it is the "first abnormality to appear and the last to leave, when the susceptible person is having difficulty with his skin." Hyperactivity to the cold pressor test to almost hypertensive levels is another evidence of vascular lability. Eczematous skin shows a swifter rate of cooling in a cool environment and a more delayed rate of warming in a warm environment than does normal skin. The intramuscular injection of histamine produces a greater increase of skin temperature at the sites of predilection for atopic dermatitis than is produced in normal persons. A normal cutaneous response occurs after the intracutaneous injection of epinephrine, but a paradoxical response follows the injection of acetylcholine. Instead of the usual red reaction to acetylcholine, a "delayed blanch" reaction occurs in susceptible persons. The explanation for this paradox is unknown, although it has been demonstrated that the addition of acetylcholine to tissue deficient in this hormone produces vasoconstriction rather than the usual dilatation.

A tendency for sweat retention in the eczematous patient often leads to miliaria and the initiation of the itch-scratch cycle. Hot humid climate is poorly tolerated. The development of cataracts occurred in 10 per cent of one series of patients with atopic eczema, especially in the most severe cases. The cataracts began in the posterior pole of the lens, in contrast with senile cataracts which began anteriorly. It was stressed that persons susceptible to atopic eczema are different physically and physiologically from the normal person. M. C.

Skin Eruptions Following the Use of Diamox. Spring, M.: Ann. Allergy **14**: 41, 1956.

Two instances of skin eruptions following the use of Diamox are reported. The first case was that of a 50-year-old female cardiac patient who was given Diamox as a substitute for a mercurial diuretic. There was no history of any prior ingestion of a sulfonamide. After receiving 375 mg. of the drug daily for 7 days, a pruritic papular eruption developed on the extremities. The medication was discontinued immediately but the eruption persisted and, in spite of the administration of antihistaminics, began to spread. During the following week, the eruption became urticarial in nature. ACTH and hydrocortisone afforded only partial relief. All medication except Gitaligin (a cardiac glucoside) was then discontinued. The eruption became erythematovesicular and generalized except for the face. A diagnosis of erythema multiforme bullosum due to mercury was made at this time and ACTH and hydrocortisone were given with good results. Shortly thereafter, signs of cardiac failure became more pronounced. Diamox was again administered and within 30 minutes the patient began to itch. Following a second dose of the drug, urticaria appeared which became more pronounced after a third dose was administered. ACTH was given with relief of symptoms. Neohydrin and Mercuhydrin were then successfully substituted for the Diamox.

The second patient was a 32-year-old man in congestive failure who had been on Neohydrin and Thiomerin. Diamox was substituted; after one week a nonpruritic papular eruption appeared on the extremities. This promptly disappeared when the drug was discontinued. About two months later, Diamox was again administered and shortly thereafter a similar eruption appeared on the chest, face, and neck. In spite of this, the drug was continued and the rash disappeared in a few days. H. F.

Exfoliative Dermatitis Associated With Hypogammaglobulinemia. Key, M. M., and Nelson, C. T.: Arch. Dermat. **74**: 333, 1956.

A 12-year-old boy with severe hypogammaglobulinemia, probably of the congenital type, developed an exfoliative dermatitis. The patient was hospitalized after the rash had been active for two months. He gave a history of repeated attacks of impetigo, otitis media, pharyngitis, sinusitis, bronchitis, and pneumonia since the age of 5 years. His infections responded temporarily to antibiotics but quickly recurred when the antibiotics were discontinued. The diagnosis of hypogammaglobulinemia had been established by electrophoretic studies and by his lack of response to immunologic stimulants. Prior to his hospitalization, he developed a scaly pruritic eruption on his face, which spread to the neck and then became generalized. He began to run a febrile course and was placed on antibiotics (penicillin, streptomycin, and oxytetracycline). At the time of hospitalization, he had a diffuse redness and scaling of the skin.

Blood studies revealed a 35 per cent eosinophilia. Hemolytic staphylococcus was cultured from the nose and *Candida albicans* from the mouth. The total protein was 7.1 Gm. per 100 c.c. but the gamma globulin was only 25 per cent of normal. Biopsy of the skin revealed an acanthotic edematous epidermis with much of the granular layer missing. Parakeratosis and superficial vesiculation were present. The papillary cutis was very edematous and showed a scattered number of eosinophils.

Following admission to the hospital, all internal medication was discontinued. Ointments containing 3 per cent chlortetracycline and 1 per cent

hydrocortisone were applied topically but produced only moderate improvement. After the patient was given 35 mg. of prednisone daily he responded rapidly, but when the dose of hormone was reduced below 20 mg. the rash flared up again. The eruption was eventually controlled by a combination of oral prednisone and 1 per cent topical hydrocortisone ointment. The authors suggest that hypogammaglobulinemia may be associated with other dermatologic conditions of the exfoliative or desquamating types. R. W.

Miscellaneous Allergies

Periarteritis Nodosa in an American Deer. Bohrod, M. G.: Arch. Path. **62**: 17, 1956.

Lesions typical of periarteritis nodosa were found in a New York State deer. The lesions occurred in the soft tissues around an old gunshot wound. A report in the literature describing an epidemic of periarteritis in a herd of deer in southern Germany is reviewed. The etiological concepts of periarteritis nodosa are discussed. The author believes that the various forms of necrotizing angiitis form a single group, the members of which overlap. Since hypersensitivity has been shown to be the etiological mechanism in one form of angiitis, it may also be the cause in the other forms. On the other hand, the disease also may be mediated by other mechanisms. The lesion found in the New York State deer may help to explain the epidemic of periarteritis nodosa described in the herd of deer in Germany and may aid in understanding the etiology of the disease in man. The frequent occurrence of periarteritis in deer may be due to a special predisposition, probably hereditary, to hypersensitivity reactions or to their arterial localization, or both. The epidemic form was probably the result of some epidemic disease in the herd which acted as a stimulus for the production of periarteritis nodosa lesions through hypersensitivity mechanisms. J. S.

Wasp Venom Allergy and Immunity. Loveless, M. H., and Fackler, W. R.: Ann. Allergy **14**: 347, 1956.

A safe immunization procedure for persons highly sensitive to the sting of the wasp was developed as the result of a study extending over a period of 3 years. Venom removed from extirpated sacs of live anesthetized wasps and other hymenoptera was used for intracutaneous, conjunctival, and passive transfer tests. On the basis of the patients' skin sensitivity, an intracutaneous immunization procedure was devised, which at first necessitated 2 or 3 annual visits. Later the procedure was changed so that the entire treatment was given during a single prolonged office visit. The contents of 6 to 9.6 venom sacs were administered intracutaneously during this visit. Following such immunization, the patient's intracutaneous and conjunctival reactions were depressed to levels approaching those observed in normal persons. Patients so treated were deliberately subjected to wasp stings and reacted in a manner similar to normal persons. Cross-neutralization tests indicated that 5 of the hymenoptera (yellow jacket, bald-faced hornet, paper wasp, honeybee, and bumblebee) possessed a common antigenic factor as well as a specific component. H. F.

The Use of L-Arterenol in a Case of Hypersensitivity to Tetanus Antitoxin. Gumpel, R. C., Kristan, J. J., and Lipton, P.: Ann. Int. Med. **44**: 406, 1956.

A 30-year-old man with a lacerated scalp was given an injection of 1,500 units of tetanus antitoxin. About one-half hour later, angioedema and urticaria

occurred. This was soon followed by abdominal cramps, vomiting, chills, and fever. The patient was hospitalized and, when it was not possible to obtain readings of his blood pressure and pulse, ACTH and l-arterenol (Levophed) were given intravenously. Within 10 minutes, there was a satisfactory rise in blood pressure. It was possible to discontinue the use of l-arterenol after nine hours. ACTH was considered to have potentiated the pressor response of l-arterenol. M. C.

Anaphylactic Shock Following Intramuscular Thiamine Chloride. Tetreault, A. F., and Beck, I. A.: Ann. Int. Med. **45**: 134, 1956.

A 57-year-old man was given an intramuscular injection of thiamine chloride. Within 5 minutes he developed dyspnea, wheezing, hypotension, and marked apprehension. He was given l-arterenol (Levophed), oxygen, and antihistamines. Within 36 hours, he made an uneventful recovery. Five years previously, following an intramuscular injection of thiamine chloride, he had developed a flushed face, palpitations, and precordial pain. M. C.

Factor in Arachis Oil Depressing Sensitivity to Tuberculin in B. C. G. Infected Guinea Pigs. Long, D. A., and Martin, A. J. P.: Lancet **1**: 464, 1956.

Guinea pigs which had been infected with B. C. G. were tested intradermally one month later with tuberculin to determine the degree of their sensitivity. The ability of various substances to depress the response to tuberculin was studied by injecting them subcutaneously 6 hours prior to a test with Old Tuberculin. The diameter of the reaction was read the next day. Single subcutaneous inoculations of arachis oil depressed sensitivity slightly but significantly. Ingestion of this material 24 hours prior to tuberculin testing also depressed tuberculin sensitivity. After purification, a nontoxic fraction was obtained which, in a dose of 0.000006 mg. per kilogram of body weight, was capable of depressing sensitivity. A comparable response was obtained when cortisone acetate in a dose of 5 mg. per kilogram of body weight was used under similar conditions. The active substance was thought to be an amine with approximately 10 to 14 carbon atoms originating from several different phospholipids with different solubilities. Vegetable lecithin from peanut or soybean likewise provided a rich source of this factor. A similar and possibly identical substance was also found in egg yolk. R. W.

The Electrocardiogram in Hypersensitivity Reactions. Contro, S., and Mond, E. Am. Heart J. **52**: 510, 1956.

Electrocardiograms made on 22 patients hospitalized for typical serum sickness over a period of 10 years were reviewed. Eleven of the patients so selected showed abnormal electrocardiographic patterns. The nature of the abnormal patterns is described in detail and is interpreted as indicating involvement of the myocardium and coronary arteries during the allergic reaction. The abnormalities usually were fleeting but persisted in one instance where pericarditis developed and in another instance where there was myocardial infarction. E. K.

The Use of an Antihistamine Agent in Preventing Serum Reactions Following the Injection of Tetanus Antitoxin. Singleton, A. O., Jr., and Little, H. M., Jr.: Surgery **40**: 784, 1956.

Despite the increased use of tetanus toxoid for immunization against tetanus, the incidence of serum reactions from tetanus antitoxin is still a major

problem. In order to study the effectiveness of oral Phenergan in the prevention of serum sickness, 250 patients requiring tetanus antitoxin in a hospital emergency service were also given Phenergan. The drug was administered in dosages of 12.5 mg. at the time of the injection of antitoxin, 12.5 mg. on the following night, and then 25 mg. each night thereafter for 7 days. A control group of 250 patients received only tetanus antitoxin. The incidence of serum reactions was 7 per cent in the group receiving both tetanus antitoxin and Phenergan and 11 per cent in the group receiving the antitoxin alone. The severity of the reactions varied from mild to severe and was similar in both groups. Since the difference between the two series was not regarded to be statistically significant, it was concluded that Phenergan did not lessen the incidence of serum reactions. J. S.

Immunological Granulocytopenia and Agranulocytosis: Clinical Aspects. Moeschlin, S.: Acta med. scandinav. Supplementum 312, Third International Congress of Internal Med., Stockholm, 1956.

A case of sulfapyridine agranulocytosis is described and is compared with 17 other cases of "immunologic" agranulocytosis previously seen by the author. Leukocyte agglutinins were demonstrated in the sera of these patients. Transfusion of agranulocytic sera into recipients of the same blood group or into laboratory animals induced a leukopenia which the transfusion of normal human serum failed to produce. An antileukocytic serum is capable of inducing agranulocytosis in guinea pigs with an increase in output of immature granulocytes. It is suggested that bone marrow changes in this form of leukopenia are the result of agglutination of leukocytes in the peripheral circulation and that the bone marrow is not the primary site of injury. A comprehensive review of the subject is included. E. K.

Severe Systemic Reactions to Para-Aminosalicylic Acid: A Case Report and Review of the Literature. Alt, W. J., and Spengler, J. R.: Ann. Int. Med. **45**: 541, 1956.

A 42-year-old man with pulmonary tuberculosis was given isonicotinic acid hydrazide (INH), 100 mg. three times a day, and para-aminosalicylic acid (PAS), 4 Gm. three times a day. About one month later he developed generalized myalgia, a pruritic maculopapular rash, and acute pharyngitis. A white cell count revealed a slight leukopenia with an absolute eosinophilia (16 per cent). The PAS was discontinued. One week later, a dose of 8 Gm. of PAS was inadvertently given. The patient suddenly developed right upper quadrant pain, generalized myalgia, and nausea. The liver, spleen, and axillary nodes were palpable. The sclerae appeared icteric and the temperature spiked to 104.8° F. An eosinophilia of 27 per cent occurred after 48 hours. By the sixth week, the liver had decreased in size and the spleen and lymph nodes were no longer palpable. A patch test with PAS was positive. The features of this case suggest PAS hypersensitivity. M. C.

Anaphylaxis

Tissue Reactions to Anaphylactic and Anaphylactoid Stimuli; Proteolysis and Release of Histamine and Heparin. Ungar, G., and Damgaard, E.: J. Exper. Med. **101**: 1, 1955.

Guinea pigs were sensitized to egg albumin or to rabbit serum. Studies with tissue slices, homogenates, and isolated organs were carried out to see

whether the proteolysis which takes place when specific antigen is added to sensitized tissues could be correlated with the liberation of histamine and heparin. Parallel studies using anaphylactoid agents, such as Tween 20, morphine, and octadecylamine, were done. Proteolysis was closely correlated with histamine and heparin release in tissues reacting to either anaphylactic or anaphylactoid agents. Fibrinolysin and streptokinase also caused histamine to be released from guinea pig lung slices, a finding which supports the concept of a proteolytic mechanism underlying histamine liberation. The addition of histamine to lung slices failed to induce a proteolytic reaction. Proteolysis could be induced as readily in guinea pig liver, which does not release histamine, as in lung tissue which does. Lung tissue released heparin in amounts comparable to those released by the liver. Inhibitors of various enzyme systems not only inhibited protein breakdown from anaphylactic and anaphylactoid injury, but they also inhibited the release of histamine and heparin. The anaphylactic and anaphylactoid agents elicited increased proteolytic enzyme (protease) activity in tissue homogenates. Extraction of enzyme from these tissue homogenates resulted in lower protease activity. Enzymatic activity fell to very low levels on the addition of activating agent to tissue extract freed of cellular debris, except for streptokinase which was equally effective in eliciting enzyme activity in the presence or absence of cellular debris. It is suggested that protease activation in tissues requires an intervening kinase system to convert a proenzyme to active protease. Tissue kinase appears to differ from serum kinase, although both are probably of importance in tissue reactions in an intact animal. E. K.

Anaphylaxis in the Mouse: Possible Relation of the Schultz-Dale Reaction to Serotonin Release. Fink, M. A.: Proc. Soc. Exper. Biol. & Med. **92**: 673, 1956.

The Schultz-Dale technique was used in experiments undertaken to determine whether or not serotonin (5-hydroxytryptamine) is the substance responsible for the specific contraction of the sensitized mouse uterus.

Serotonin was dissolved in Ringer's solution and the reactivity of normal and sensitized uteri was studied. It was found that a dose of 0.05 γ/ml. of bath was sufficient to produce a good contraction in normal or sensitized uterine strips. The addition of lysergic acid diethylamide (LSD) in a concentration of 3 γ/1 was sufficient to prevent a reaction to 0.05 to 0.1 γ/ml. of serotonin. Reserpine in a concentration of 5 mg./1 prevented a reaction to 0.05 to 0.1 γ/ml. of serotonin. Mice sensitized to egg albumin were used in these experiments. Positive reactions to egg white were demonstrated on 2 of the 4 strips into which each of the uteri was divided. Complete inhibition of anaphylaxis in the presence of LSD or of reserpine was found on the other 2 strips of the same animals. LSD and reserpine uniformly abolished the reaction to serotonin but not that to acetylcholine. Serotonin is the only drug known to be inhibited by LSD and reserpine.

It was shown that the isolated uterine strip is sensitive to 0.05 γ/ml. of serotonin, while a concentration of 50 γ/ml. of histamine is necessary to produce a reaction. Thus, the isolated strip of the mouse is 1,000 times more sensitive to serotonin than to histamine. The tissues of the mouse contain enough serotonin to produce the anaphylactic response, but probably lack the amount of histamine necessary to induce a reaction. Antihistamine drugs do not inhibit anaphylaxis in the intact mouse or in isolated uterine strips. These findings support the hypothesis that the anaphylactic reaction in the mouse is dependent on the release of serotonin and not of histamine.

S. Stousland.

The Immunologic Response of Mice From Stocks Resistant and Susceptible to Acute Disseminated Encephalomyelitis. Olitzky, P. K., and Lee, J. M.: J. Lab. & Clin. Med. **45**: 81, 1955.

Studies were made on the immunologic responses of mice from stocks which were resistant or susceptible to the development of acute disseminated encephalomyelitis following inoculation of normal brain tissue mixed with a Freund-type adjuvant In agglutination and precipitation tests in which typhoid vaccine and horse serum were the antigens, no difference was found in the serum titers of the resistant or susceptible strains of mice. The results of the anaphylaxis studies, however, were quite different. Seventy per cent of the susceptible strain died in anaphylactic shock, whereas only 6 per cent of the resistant strain died in shock. E. W.

Pharmacology, Physiology, and Pathology

A Broncho-constrictor Factor in Cigarette Smoke. Loomis, T. A.: Proc. Soc. Exper. Biol. & Med. **92**: 337, 1956.

Mature guinea pigs were anesthetized and into their tracheas special Y-shaped cannulas were inserted which were connected to a positive pressure artificial respirator. Attached to this were cigarettes which were smoked by a mechanical Robot-Smoker. One arm of the cannula was connected to a manometer so that tracheal pressure could be recorded. After control inflation pressure curves were taken, six brands of cigarettes were tested on separate guinea pigs. The chief effects of cigarette smoke on pulmonary inflation pressure were a more rapid increase in inflation pressure in the middle of the cycle and a fall in inflation pressure before the end of the inflation cycle. This type of effect was interpreted as being the result of a broncho-constrictor action of the cigarette smoke. The maximum effect occurred when the cigarette was smoked down to 5 cm. The least effect was noted when the cigarette was nearly full length, that is, 8.4 cm., indicating the importance of the length of the cigarette as a factor in filtering the smoke. The presence of a filter tip failed to alter significantly the response in the lung as compared to cigarettes with a plain tip. "Denicotinized" cigarettes uniformly showed less effect than other brands.

Intracardiac injection of atropine blocked the pulmonary response to acetylcholine and nicotine, but failed to block the response to cigarette smoke. This indicated that the broncho-constrictor action of cigarette smoke is not due to nicotine. Further studies showed that the cigarette smoke response was rapidly abolished by the inhalation of amyl nitrite. The pulmonary response in guinea pigs to cigarette smoke is felt to be due to airway hindrance caused by a narrowed caliber of the bronchioles. B. S.

Mechanism of Diurnal Eosinophil Rhythm in Man. Kaine, H. D., Seltzer, H. S., and Conn, J. W.: J. Lab. & Clin. Med. **45**: 247, 1955.

Total eosinophil counts were made every 2 hours over a 24-hour period in 6 normal subjects and on 7 patients with Addison's disease. All the patients were maintained on desoxycorticosterone acetate in doses of 2 mg. administered buccally after breakfast and after dinner. Studies on normal patients indicated a maximal fall in total eosinophils between 6 A.M. and 2 P.M., followed by a gradual rise toward or above the 6 A.M. value. When 7 patients with Addison's disease were given 2.5 mg. of cortisone orally every 3 hours for 36 hours, counts during the last 24 hours showed but slight variation. When 3 patients with Addison's disease received 10 mg. of cortisone

at 8 A.M. and 5 mg. at 2 P.M. and 8 P.M., their eosinophil curves were practically flat. Four patients with Addison's disease who were given 25 mg. of cortisone at 6 A.M. showed eosinophil curves strikingly similar to those of normal subjects. The maximal fall, however, was greater in the patients (46 per cent) than in the normal subjects (32 per cent). Two patients who received no cortisone showed no significant fluctuation in eosinophil counts throughout the 24-hour period of observation. Two patients with Addison's disease, who were receiving 2.5 mg. of cortisone orally every 3 hours, were subjected to a 4-hour ride on a stationary bicycle during the early morning. The superimposition of hard and prolonged exercise did not produce a decrease of circulating eosinophils. These results seemed to indicate that the normal diurnal eosinophil rhythm is not an example of the "permissive activity" of adrenal steroids. These findings also suggest that "under normal circumstances a sharp change in the concentration of blood 17-hydroxycorticoid affects eosinophils more importantly than does the absolute concentration." E. W.

Absorption of Inhaled Hydrocortisone. Cotes, P. M., McLean, A., and Sayer, J. B.: Lancet **2**: 807, 1956.

The urinary excretion of 17-hydroxycorticosteroids was studied in two normal male subjects before and after the inhalation of hydrocortisone. Control studies were made with formolized starch powder. Hydrocortisone was used in both the acetate and the free alcohol form and the mean particle size of each form was less than 5 μ in diameter. Patients inhaled the contents of 3 capsules, each containing 15 mg. of hydrocortisone, during a 2- to 3-hour period. Inhalations of the hormone or of the placebo were always carried out at the same time of day. The urinary excretion of 17-hydroxycorticosteroids increased in the 12-hour period immediately following inhalation of the hormone but not of the placebo. Approximately equal rises in urinary excretion of 17-hydroxycorticosteriods were observed following inhalation of 45 mg. of hydrocortisone or the ingestion of 40 mg. of hydrocortisone. R. W.

The Effect of Obstruction to Breathing on the Ventilatory Response to CO_2. Cherniack, R. M., and Snidal, D. P.: J. Clin. Invest. **35**: 1286, 1956.

Ventilatory responses to CO_2 inhalation were determined in normal and in emphysematous persons. Emphysematous subjects responded less to CO_2 stimulation than did normal subjects. Normal subjects with a decreased maximum breathing capacity produced experimentally by increased airway resistance also showed a reduced responsiveness to CO_2 comparable in degree to that of emphysematous subjects. When bronchodilators increased the maximum breathing capacity of emphysematous subjects, there was a concomitant increase in CO_2 ventilatory response. E. K.

A Comparison Study of Drugs in Experimental and Clinical Auricular Fibrillation. Dick, H. L. H., and McCawley, E. L.: Am. Heart J. **60**: 442, 1955.

Milligram for milligram, Benadryl and Banthine were found to be as effective as quinidine in converting or preventing experimental auricular fibrillation in dogs. In 17 human beings in auricular fibrillation, 11 were converted to sinus rhythm by Benadryl. In another group of 17 fibrillators, 10 were converted by quinidine. In one patient, conversion was attained by

a combination of Benadryl and quinidine when neither drug alone had been effective. Banthine had no effect on clinical fibrillation. The dosage of Benadryl varied from 100 to 300 mg. intravenously. One patient was given a 400 mg. dose. In another case, the drug was discontinued, because of side effects, after 180 mg. had been administered. Muscle twitching was an indication of toxicity. In a patient with myocardial infarction who developed ventricular tachycardia, Benadryl, 100 mg., was given by intravenous infusion. Within 15 minutes after the procedure started the ventricular tachycardia converted to auricular fibrillation and 10 minutes later to normal rhythm. In the doses used in human beings the QRS complex was not changed by Benadryl; there was an unexpected decrease in Q-T interval. Bundle branch block and other changes in myocardial conduction similar to those seen during quinidine therapy were produced by Benadryl. E. K.

Immunology

Studies on the Cellular Transfer of Tuberculin Sensitivity in the Guinea Pig. Metaxas, M. N., and Metaxas-Buehler, M.: J. Immunol. **75**: 333, 1955.

It is generally assumed that the tuberculin reaction is the result of the combination in vivo of tuberculin with specific antibody. Chase had shown in 1945 that tuberculin sensitivity could be passively transferred to normal animals by the injection of living cells derived from actively sensitized animals. The present study deals primarily with the latent period in passively induced tuberculin sensitivity in the guinea pig. The results point to the possibility that it is the transferred cells themselves that respond in tuberculin tests performed on the recipient animals.

Peritoneal exudate cells from donors sensitized with BCG were given intravenously to animals which were then tested at once by intradermal, intracorneal, or intraperitoneal injections of tuberculin. Typical local or systemic reactions developed without a preceding latent period. They started in 4 to 8 hours, which was the same as the reacting time observed in the donors. When exudate cells and tuberculin were mixed and injected into the skin, positive results were also obtained. When cells were injected intravenously into animals which had been skin tested with tuberculin 3 to 24 hours earlier, typical local reactions developed at the test sites. When the cells were given intraperitoneally, however, cutaneous reactions did not develop until about 20 hours after cell transfer. Guinea pigs receiving simultaneous intraperitoneal or intravenous doses of cells and tuberculin started to develop symptoms of shock after 3 to 4 hours and died from 2 to 10 hours later. Minimal skin reactivity was induced by the intravenous injection of about 0.05 ml. of moist packed cells and a maximal sensitivity was obtained with 0.3 ml.

Transferred tuberculin sensitivity did not last longer than 4 or 5 days. Mild freezing or heating destroyed the sensitizing capacity of the cells. On the basis of these results, it is suggested that the response in these passively sensitized animals was the result of direct interaction between the tuberculin and the transferred cells. S. Stousland

Studies on the Antigenicity of Modified Fluid Gelatin. Maurer, P. H., and Lebovitz, H.: J. Immunol. **76**: 335, 1956.

Modified fluid gelatin (MFG) has been shown to be an effective plasma volume expander in experimental animals and man. MFG was prepared by

reacting the gelatin with succinic anhydride and isolating the protein derivative at its isoelectric point. Twenty human volunteers were given 5 daily intramuscular injections of various amounts of MFG. Blood samples were taken and intracutaneous tests were performed with the MFG prior to immunization and again three weeks after the last injection. Precipitating antibody failed to appear in any of the subjects. The intracutaneous test reactions were all negative. When mixtures of decomplemented human antisera and known amounts of MFG were added to rabbit anti-MFG sera, the anticipated amounts of anti-MFG antibody were precipitated. This indicated that coprecipitating antibody was not produced in human beings in response to the MFG injections.

Rabbits were injected with MFG in a water-in-oil adjuvant mixture, MFG in saline solution, or MFG in the form of an alum precipitate. Detectable antibodies were produced only with the adjuvant mixture. From hydroxyproline analyses of the specific precipitates of MFG and its antibody, it appeared that the antibodies produced by the MFG injections were antibodies to MFG and not to possible trace contaminants in the MFG.

Cross reaction studies done with various succinylated derivatives of MFG bovine gamma globulin, bovine serum albumin, rabbit gamma globulin, and beef and rabbit gelatin against the anti-MFG sera revealed that the serologic specificity was directed against the introduced succinyl groupings. Cross reactions with esterified derivatives of MFG were studied to explore further the specificity of the determinant group in MFG. The results indicated that the carboxyl groups of MFG were important, though not the sole, determinants for the antigen-antibody reaction.

The MFG-anti-MFG reaction was found to be inhibited by various dibasic acids and related substances. These salts failed to inhibit the bovine serum albumin—rabbit-anti-bovine serum albumin system, even when high concentrations were employed. A definite solubilizing effect on MFG-anti-MFG specific precipitates by the salts of the acids was found. The marked solubilizing effect of succinic and maleic acids and succinimide may be related to the structure of the determinant groupings in MFG.

The authors suggest that further studies with MFG are indicated before definite conclusions can be reached as to its antigenicity in man. B. S.

Enhancement of Immunization Response by Phosphorylated Hesperidin. Moss, J. N., Beiler, J. M., and Martin, G. J.: J. Immunol. **76**: 363, 1956.

Viral antigens and diphtheria and tetanus toxoids were prepared in saline, in phosphorylated hesperidin solution, and in water-in-oil emulsion. Rabbits, mice, and guinea pigs were immunized with these preparations. The immune response was measured by hemagglutinin-inhibition tests when viral antigens were employed and by protection tests when toxoids were employed. The immune response to antigens prepared in phosphorylated hesperidin was found to be increased and comparable to that obtained with antigens prepared in water-in-oil emulsion. The adjuvant action of phosphorylated hesperidin appears to be due to the production of a depot effect. B. S.

Electrophoretic Distribution of Serum Proteins in Rabbit, Guinea Pig and Rat Following BCG Administration. Hudgins, P. C., Cummings, M. M., and Patnode, R. A.: Proc. Soc. Exper. Biol. & Med. **92**: 75, 1956.

The effects of BCG inoculation on the serum proteins were compared in rabbits and guinea pigs, which are susceptible to tuberculosis, and in rats, which are naturally resistant to the disease. Sera were obtained before and

four weeks after the intraperitoneal injection of BCG. Electrophoretic studies revealed a significant elevation in total protein and gamma globulin in the postinjection sera of rabbits and guinea pigs, but not of rats. Guinea pig sera also showed an increase in concentration of alpha-1 globulin, while rat sera showed a decrease in this fraction. A relative decrease in albumin concentration was found in rabbit and guinea pig postinoculation sera. The serum protein changes in guinea pigs and rabbits were similar to those previously found in tuberculous animals of these species. The lack of response in the rat is probably related to this animal's native resistance to infection. B. S.

The Production and Identification of Antibodies to Insulin and Their Use in Assaying Insulin. Arquilla, E. R., and Stavitsky, A. B.: J. Clin. Invest. **35**: 458, 1956.

Insulin was coupled to red cells by a method using bis-diazotized benzidine. Antibodies to insulin could be detected by using these cells in hemagglutination and hemolysis reactions. Rabbits could be regularly sensitized to insulin by 6 to 10 intravenous injections of at least 2.5 mg. alum-precipitated insulin given over a period of 16 to 202 days. Antibodies generally appeared 2 to 6 months after the first injection of antigen. Anamnestic responses were observed in all previously immunized rabbits. Precipitins were not demonstrable even in the presence of high hemagglutination titers. Negative skin reactions were obtained on both direct and passive transfer testing.

Of 23 diabetics tested, 11 were found to have circulating anti-insulin antibodies. Seven patients who had received 120 to 2,000 units of insulin daily showed these antibodies. The other 4 patients with antibodies had received 70 to 90 units of insulin daily. Insulin antibodies were absent in 9 diabetics, including one who was receiving 100 units of insulin daily and in 4 who were untreated. The presence of antibody was questionable in 3 instances. E. K.

Miscellaneous

Considerations of Special Interest to the Allergist on the Composition and Production of Poliomyelitis Vaccine. Bierly, M. Z., Jr.: Ann. Allergy **14**: 349, 1956.

Poliomyelitis vaccine is prepared by growing representative strains of 3 known immunologic types of polio virus on tissue cultures of monkey kidney epithelial cells. These cells are grown in a synthetic medium (199) containing a mixture of amino acids, salts, vitamins, minerals, and phenolsulfonphthalein, plus 0.5 per cent horse serum. Penicillin G, neomycin, and dihydrostreptomycin are added to the medium in amounts sufficient to bring their concentrations in the mixture to 200 units, 0.1 mg., and 0.2 mg. per cubic centimeter, respectively. The mixture of tissue cells, medium, and antibiotics is incubated for approximately 7 days to allow for sufficient growth of tissue cells. The medium is then drawn off and the remaining sheets of cells are washed twice with Hank's balanced salt solution. This washing and the subsequent restoration of volume reduce the horse serum content of the mixture to less than 1 part in 5,000,000 and the antibiotic content to approximately 0.003 unit per cubic centimeter of penicillin, 0.0000015 mg. per cubic centimeter of neomycin, and 0.000003 mg. per cubic centimeter of dihydrostreptomycin. Fresh medium 199 is added and the cells are then inoculated with a specific amount of seed polio virus.

Since at the time of virus infection of the culture it is necessary to restore the antibiotic content to prevent bacterial contamination, a solution of polymyxin B and dihydrostreptomycin is added to bring the final concentrations to 50 units of polymyxin B and 0.1 mg. of the dihydrostreptomycin per cubic centimeter. The polymyxin B is substituted for penicillin in this preparation of vaccine (Wyeth) because it is seldom used in clinical practice and is considered to be almost nonantigenic, although it is a potent antibiotic. After inoculation, the mixture is again incubated, titrated, and filtered. Inactivation is accomplished with formaldehyde solution in a final concentration of 1:4,000. After testing for potency, sterility, identity, and the presence of other pathogens, the formaldehyde is neutralized with sodium bisulfite and preservatives are added.

Reactions following the use of polio vaccine are uncommon and, to date, have been of a mild character. It is unlikely that they are caused by the low-molecular-weight amino acids in the medium or to its horse serum content (1-5,000,000). The phenolsulfonphthalein and the preservative are presumably nonantigenic and the formaldehyde, which may be allergenic, has been inactivated. The possibility of renal damage or sensitization by the kidney tissue cells used in the preparation of the vaccine has been considered, but no complement-fixing antibodies have been found and no clinical evidence of renal damage has been reported. In addition, dermal sensitivity has not been demonstrated by intracutaneous tests with kidney culture and there is no evidence of Rh sensitization having been produced by the vaccine. Reactions to the vaccine may be expected to occur to about the same degree as reactions to other biologicals, and only continued use will reveal the actual allergenicity of the product. H. F.

Prevention of Acute Respiratory Illness in Recruits by Adenovirus (RI-APC-ARD) Vaccine. Hilleman, M. R., Stallones, R. A., Gauld, R. L., Warfield, M.S., and Anderson, S. A.: Proc. Soc. Exper. Biol. & Med. **92**: 377, 1956.

A type 4 and a type 7 strain of the RI virus family were used to prepare adenovirus vaccines. These strains were cultured on monkey kidney epithelial tissue. The filtered virus suspensions were then rendered noninfectious by treatment with formalin. After a series of safety and sterility tests, the vaccines were used for animal and human experiments. Guinea pigs were injected with 0.25 ml. of inactivated aqueous monovalent vaccine or with 0.50 ml. of adjuvant-vaccine emulsion. Blood specimens were taken four weeks later. Negligible amounts of neutralizing antibody resulted from the injections of the aqueous monovalent vaccine. The neutralizing antibody titer resulting from the injection of the adjuvant preparations was 1:32. Type 4 vaccine in adjuvant was the only preparation which stimulated the formation of complement-fixing antibodies.

One milliliter of an RI vaccine preparation, containing both types 4 and 7, was injected intramuscularly into 12 human volunteers. Increases in neutralizing antibody titer were noted against homotypic 4 and 7 virus and also against heterotype 3. The increases in titer were of the order usually observed following natural infection with these viruses. In several volunteers 2 additional injections of vaccine were administered, but no further increases in neutralizing antibody titer were noted. The complement-fixing antibody response occurred infrequently and was of low titer. These studies indicated that the neutralizing antibody response to the aqueous vaccine is much greater in man than in guinea pigs.

Soldiers beginning their basic training at Fort Dix, New Jersey, were given two weekly intramuscular injections of 1 ml. of bivalent RI virus vaccine or of a placebo. Blood samples were drawn prior to the injections and three and seven weeks later. Soldiers who were hospitalized with any acute respiratory infections were bled on admission and again three weeks later and throat washings for virus recovery were collected. During the period of observation, 10.3 per cent of the 311 soldiers receiving vaccine were hospitalized for acute respiratory infections as compared with 28.4 per cent of the 313 soldiers receiving the placebo. When the cases occurring during the first week after the initial injection were excluded, only 4.8 per cent of the vaccinated men were hospitalized as compared with 23.8 per cent of the controls. From the second to the fourth week after inoculation, there were about eleven times as many men hospitalized in the control group as in the vaccinated group. During the last four weeks of basic training there were very few cases of respiratory illness, because the supply of susceptible patients was largely depleted. There were no untoward effects noted as a result of vaccine administration.

The virus isolation and serologic studies showed that approximately 9 of every 10 cases of acute respiratory infection admitted to the hospital during the period of investigation were of RI viral etiology, indicating that the vaccine was tested during the course of an epidemic of RI virus infection. Of the RI viruses isolated, 59 per cent were type 7 and 41 per cent were type 4.

The authors conclude that this vaccine is highly effective against acute respiratory illnesses caused by viruses of the RI (adenovirus) family. They suggest that better results could be expected if the vaccine were administered at the time the recruit is first inducted into the Army or as soon as possible after his arrival at the training base. B. S.

Corticotropin-Zinc Hydroxide Evaluation in the Therapy of Certain Collagen Diseases. Banghart, H. E., and Watanabe, R. K. D.: Am. Pract. **7**: 1957, 1956.

In a study of a series of patients suffering from various collagen diseases, ACTH was found to be a much more effective therapeutic agent than cortisone or hydrocortisone. In comparing ACTH gel with zinc ACTH, it was found that only two-thirds as much of the latter preparation was required to obtain equivalent suppression of symptoms. The duration of action of zinc ACTH appeared to be longer than that of the gel. Similar side effects were obtained with both preparations but, of the two, the zinc ACTH seemed to have less effect quantitatively on serum electrolytes and less tendency to produce diabetes and gastric ulcers. H. F.

A New Diluent for Eosinophil Counts. Tannen, J.: Am. J. Clin. Path. **26**: 197, 1956.

The two diluents which are now commonly used for eosinophil counts are made from an acetone base with eosin or magdala red and from an aqueous propylene glycol base with methylene blue and/or phloxine. A new diluent is described which consists of an aqueous base with neutral red iodide and sodium hydroxide. This diluent was compared with the others in counts in 26 persons. It was found that the new diluent was more stable, was less likely to lyse eosinophils, and acted more rapidly than the older diluents. Because all cells other than eosinophils are lysed, the reading error is reduced when the new diluent is employed. E. K.

Fatal Vaccinia Associated With Cortisone Therapy. Olansky, S., Smith, J. G., Jr., and Hansen-Pruss, O. C. E.: J. A. M. A. **162**: 887, 1956.

A 42-year-old woman with chronic lymphocytic leukemia, who was on intermittent therapy with triethylene melamine and cortisone, was given a course of smallpox vaccinations for herpes simplex of the lip. Primary reactions to vaccinia occurred. During the next few weeks, vesicles appeared about the groin, arms, trunk, and legs. The original vaccination site gradually extended down the arm and around the shoulder and became necrotic. The white blood count was 6,000 with abnormal lymphocytes. The gamma globulin was slightly lower than normal. Chest x-ray examination showed a diffuse interstitial infiltration of the lungs. Despite treatment with antibiotics, gamma globulin, and blood transfusions, the patient died 49 days after the initial vaccination. In reviewing the literature, it was noted that 3 deaths had occurred among children who contracted varicella while receiving cortisone for other diseases. Autopsies in these cases revealed varicella lesions in all organs. M. C.

Perforated Duodenal Ulcer Complicating Prednisone Therapy. Fentress, V., Firnschild, P., and Reveno, W. S.: New England J. Med. **254**: 657, 1956.

Among 18 arthritic patients treated with prednisone, three with peptic ulcers were encountered. One of these perforated. This patient, a 21-year-old white woman with rheumatoid arthritis, had been treated over a long period of time with combinations of cortisone, Acthar Gel, antibiotics, salicylates, and phenylbutazone, with unimpressive results. After a course of Acthar Gel, which was administered in gradually diminishing doses over a 6-week period, this patient was put on prednisone in doses ranging up to 25 mg. per day. After three months of this therapy, she was admitted to the hospital with a diagnosis of perforated peptic ulcer. On exploration, a perforation was found in the anterior wall of the first portion of the duodenum. After eight weeks, x-rays showed healing of the ulcer. It was suggested that preliminary gastrointestinal x-ray studies be instituted in all patients in whom long-term steroid therapy is contemplated. E. W.